L. (5)
د/ أمـــل

Cholinergic Antagonists

نبتدي على بركة الله
يلا ...

= cholinolytics
= parasympatholytics
= cholinoceptor antagonist

* مهمة اوي التسميات دي *

زي الـ agonists، الـ antagonists برده

divided into muscarinic & nicotinic subgroups on the bases of their specific affinity to receptors.

Cholinolytics
- Antinicotinic
  - Ganglionic blockers (↓ clinical uses)
  - Neuromuscular junction blockers
- Antimuscarinic agents (↑ clinical uses)

عادة لما يتقول cholinolytics بيكون كلامنا على الـ antimuscarinic agents.

* Nicotinic Receptor

(1)- ganglionic R < symph. / Parasymph.

(2)- Nm. neuromuscular junction (somatic) .... نتكلم عن دي الاول

(3) - Sweat gland at synapse

Parasymp. — (Nn) — ACh — (M)
(sym, Pl) — (Nn) — sweat gland
(Nn)
Somatic — (Nm)

Anti muscarinic Agents

1. mainly Atropine (prototype)
   (d.L hyoscyamine) → Racemic mixture
   found in Datura stramonium
2. scopolamine
   (L-hyoscine) levo
   found in Hyosyamus niger

I Antimuscarinic agents

ة cognosy — شـــوية

* The naturally occuring muscarinic receptor antagonists :
  atropine (prototype) → بجيكم واحد بس
  & Scopolamine
→ are alkaloids of the belladonna (Solanacae) plants.
- Preparations of belladonna have been used for many centuries by physicians.

- Atropa belladonna

قاطعة ↓ Atropa = cuts the thread of life

↓ belladonna = women & dilate their pupils

* Atropine (d,l hyosciamine [racemic mix.]) is also found in Datura stramonium, also known as Jamestown or jimson weed.

* Scolopamine (l- [levo] hyoscine) is found chiefly in Hyosciamus niger (henbane)

* A variety of semisynthetic & fully synthetic molecules have antimuscarinic effects.

* Pharmacokinetics of Anti muscarinic

3ry Alkaloids →
↑ lipiophilic →
unIonized form →
↑ absorpTn
So rapidly dirstributed in body and CNS. As They Cross BBB

eg Tropicamide
Benztropine

4ry Alkaloids →
Polar Compd →
Ionized form →
↓ absorpTn So poorly Taken up by ↓ Brain at in CNS

eg Ipratropium
Propantheline

Atropine
→ Disappear rapidly from ↓ Blood
half life → 2hrs
→ ∴ ↓ Drug effect ↓ rapidly in organs
except in eye → 72 hrs why ??
due To [Passive mydriasis]
unresponsive To light

Atropine → Radial muscle → Passive mydriasis

Tropicamid

@ Kinetics :

اللى هو تأثير الجسم على الدواء ، اول ما نشوف
العنوان ده ← تفكر فى ال absorption, distribution كده يعنى ...

↑ lipophilic (non Ionized)
↑ absorption

* The natural alkaloids and most 3ry antimuscarinic drugs (tropicamide, benztropine) are well absorbed from the gut and conjunctival membranes (eye) ⟶ widely distributed in the body & rapidly distributed into the CNS (as it can cross BBB)

كل ده احنا عارفينه لان ال 3ry بيبقى more lipophilic وهو ده
اللى بيحصله ال absorption ، لكن

* In contrast, the 4ry derivatives (Ipratropium, propantheline) are poorly taken up by the brain & therefore are relatively free - at low doses - of central effects.
مش بيوصل لـ CNS

* Atropine disappears rapidly from the blood, with a half life of 2hrs
مش بيفضل كتير فى الدم

• The drug's effect declines rapidly in all organs except the eye (72 hrs)
طب اشمعنى بقى ؟!
الاول ، الادوية دى parasympatholytics يعنى هتعمل ايه فى العين ؟!

mydriasis المفروض (Diltation)
صح ؟!

هى فعلا بتعمل كده بس بتعمل نوع اسمه Passive mydriasis يعنى
mydriasis بس unresponsive to light ، يعنى لما تتعرض لضوء

Non Selective Blocker
$M_1, M_2 - M_3 - M_4 - M_5$

* MOA of ATropine

→ Competetive blocker of muscarinic R
↓
overcomed by ↑ Dose of muscarinic Agonist

→ Tissues highly sensitive for ATropine
Salivary - bronchial - sweat
But Parietal cells (Stomach) ↓ senstivity

ال pupil مش هتضيق ، فالانسان ده مش هيقدر يفتح عينه فى الشمس وهو ده اللى بيحصل للناس اللى بتروح تكشف قاع العين بيقعد ٣ ايام تقريباً مش عارف بيشوف كويس وده لان ال atropine بيفضل كتير فى العين.

• فى النوع التانى اللى هو ال active mydriasis يعنى هيحصل mydriasis بس هيبقى responsive to light ، ازاى ؟!
by constriction of constrictor pupil muscles.
أمال ايه العضلات اللى بتعمل اصلاً ال mydriasis ؟!
→ Radial muscles are resp. for mediasis

ⓑ MOA:

* Atropine and related compounds cause competitive blockade of muscarinic receptors
So blockade by small doses of atropine can be overcomed by a larger conc. of muscarinic agonist.

* Tissues most sensitive to atropine are: the salivary, bronchial & sweat glands.
- Gastric parietal cells are the least sensitive.

* Atropine doesn't distinguish between M_1, M_2 & M_3 receptors (i.e. Non selective blockade)
Other antimuscarinic drugs have moderate selectivity for one or another of these subgroups.

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effect of Atropine :-

① CNS

- (Atropine) Therapeutical Dose (1mg) → mild stimulatn of medulla and higher cerebral center
- ↑ Dose → irritability (عصبي!) & Hallucinatn
- ↑↑ Dose (still ↑ Dose) → stimulatn followed by inhibitn → respiratory failure → Coma

(Scopolamine) CNS Depressant

Drowsiness نوم , Amnesia فقدان ذاكرة

III of Parkinsonism ??

III " motion sickness ??

② eye

① Passive mydriasis (unresponsive to light)

② cycloplegia (loss of accommodatn of near vision)

③ ↑ Dangerous in glucoma patients as ↑ aqueous humer entrapement

④ Reductn of Lacrimal secretion So Sandy eye, Dry eye

③ GIT

- ↓ Tone & ↓ motility → ↑ gastric empty time
- ↓ salivary secretn
- (Pirenzepine) Selective M_1 blocker ↓ gastric ā secretn
- (Atropine) ↓ Thermo regulatory → ↓ sweating → Atropine fever

④ CVS

- ↓ Dose Atropine: Brady cardia (Block presynaptic Receptor → Ach↑ → ↓ Rate)
- ↑ Dose Atropine: Tachy cardia (Block Postsynaptic Receptors M_2) Ach effect blocked

⑤ Respiratory system

- Broncho Dilating
- reduce in secretn (M_3)

⑥ Urinary Tract

↓ muscle Tone and ↓ amplitude of muscle contractn of ureter, Bladder. (M_3)

(C) Pharmacological Properties :

هنشوف الـ effect بتاعهم على :

1. CNS
2. Eye
3. GIT
4. CVS
5. Respiratory system.
6. Urinary tract

1. CNS :

الحاجات دى كلها parasympatholytics يعنى عكسها يبقى لو الـ parasympathatic بتعمل relaxation او بتدى الـ effects بتاعت الـ rest يبقى الـ reagents دى هتدى عكس الـ effects دى.

* Atropine in therapeutic doses (1mg) causes only mild excitation as a result of stimulation of the medulla and higher cerebral centres.
- Toxic doses lead to restlessness, irritability & hallucinations.
- With still larger doses → stimulation is followed by depression → leading to circulatory collapse, respiratory failure & coma.

* Scopolamine → causes CNS depression manifested as drowsiness (احساس بالنوم) and amnesia (فقدان الذاكرة)

drowsiness
& amnesia

(الشلل الرعاش)
- Scopolamine is used for Parkinsonism as it results from excess cholinergic activity because of deficiency of dopaminergic activity in the basal ganglia striatum system.

- ايه ده؟!!

* However, in the presence of severe pain → the same doses of scopolamine can occasionally cause excitment, restlessness & hallucinations.

* Motion sickness → involve muscarinic cholinergic transmission

→ يبقى اقفل ال receptors دى ← فاامنع ال motion sickness

∴ Scopolamine is often effective in preventing or reversing these disturbances.

2. EYE:

احنا كنا اتكلمنا عنها شوية مع ال atropine لما قلنا إنها بتعمل ال passive mydriasis ← تعالوا نقول الكلام ده تاني ونزود عليه حبة حاجات...

1) Passive mydriasis (dilation of the pupil) → unresponsiveness to light (photophobia) → يعني بيخاف من الضوء لأنه مش بيقدر يفتح عينه في الضوء

2) Cycloplegia (= loss of accomodation for near vision)
↓
ده اللي بتعمله ال parasympathatic وانا بقفلها ← فهو وقف ده

3) In patients with glucoma → IOP (Intraoccular pressure) may rise dangerously.

طب ليه؟!
احنا كنا قلنا المحاضرة الرابعة ان ال parasympathatic بتعمل myosis يعني contraction في ال circular وال ciliary m. وقلنا ان ده بيفتح ال canal علشان ال aqueous humor يعرف يطلع ← حلو كده؟!

انا لما اقفل ال receptors دي بقى ← كل اللي فوق ده مش هيحصل يبقى مش هيعرف يخلص من ال aqueous humor يبقى ال IOP هتزيد.

طب لو هو عنده glaucoma يعني اصلاً مش بيعرف يخلص كويس من ال aq. humor ← يبقى لما اقفل ال receptors لما ← البنا هتبوظ خالص ← يبقى ال IOP هيزيد اوي.

حاولوا تفسروا كل حاجة كده، ما تحفظوش وخلاص...

4) Reduction of lacrimal secretion leads to dry or "Sandy" eyes.

يعني هتحس كأن فيه رملة في عينه.

3_ GIT:

* ↓ tone & motility ⟶ ∴ gastric emptying time is prolonged & intestinal transit time is lengthened.

مفروض تكون عارفين ليه؟

هتفكر بنفس الطريقة ... دي parasymp.rec ← يبقى هتعمل

ايه لل GIT؟ ← يبقى لما اقفلها ← هيحصل ايه؟!

* Salivary secretion is significantly reduced, however, gastric secretion is blocked less effectively.

* Pirenzepine (Selective M_1 blocker) & a more potent analog ⟶ ↓ gastric acid secretion with fewer adverse effects of atropine.

* Atropine suppresses thermoregulatory sweating & muscarinic receptors at the end of sympathatic cholinergic fibres innervating sweat glands ⟶ "atropine fever"

تعالوا نفهم النقطة الاخيرة دي الي سنوية ...

فاكرين احنا كنا قلنا قبل كده ان ال sweat gland فيها استثناء

انها sympathatic بس cholinergic (muscarinic) receptors

فال sympathatic effect هكيون ↓ blood flow to skin يعني ↓ sweating

وال parasympathatic effect هكيون العكس ← يعني هيحصل sweating
وده مهم جداً علشان يضبط درجة حرارة الجسم (thermoregulatory)

فلما اقفل ال receptors دي ← هامنع ال sweating وبالتالي
درجة حرارة الجسم هتعلى اوي وده اسمه ← Atropine fever.

4- CVS : (Cardiac Vascular system)

- low doses → initial bradycardia as it inhibits presynaptic receptors on vagal fibres

هو لما يقفل ال presynaptic receptors اللي بتقلل خروج ال Ach
← يبقى ال Ach هيزيد ← اللي هنا على القلب بيقلل
ال rate ← فتقل bradycardia
طب لو زودت الجرعة !؟

- larger doses of atropine → cause progressively ↑ tachycardia by blocking vagal effects on M_2 receptors (postsynaptic) on the SA nodal pacemaker

يعني لما الجرعة بتزيد ← بيشتغل على ال M_2 recep دي postsynaptic
يعني لما يقفلها ← هيقفل تأثير ال Ach ← اللي المفروض يقلل
ال rate ← يبقى ال rate هيزيد ← يعني هيعمل tachycardia

انا عارفة اني بطول اوي عليكم ← بس معلش علشان لازم
تكونوا فاهمين كويس اوي ← استحملوني معلش.

5. Respiratory System:

- Both smooth muscles & secretory glands of the airway receive vagal innervation & contain muscarinic receptors.

- Atropine causes → bronchodilation & reduction of secretion (M_3 receptor)

وده لأن الـ paraymp. بتعمل bronchoconstrictⁿ وبتزود الـ secretions
يبقى ده هيعمل العكس على طول ..

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6. Urinary tract:

- M_3 receptor mediate detruser muscle contraction.

∴ Muscarinic antagonists → ↓ the normal tone & amplitude of contractions of the ureter & bladder.

طب احنا كده خلصنا الـ Pharmacological effects تعالوا
نشوف الـ Therapeutic uses بتوعه ممكن استخدمها
في إيه ......

* Therapeutical uses :-

1. Bronchial asthma (COPD) chronic obstructive Pulmonary Disease
   - Bronchodilatn so used in cold mixture as anti Histaminic
   - Ipratropium ⇒ inhalatn as have ↓ adverse effect Than Atropine in mucociliary clearance as it is 4ry.

2. overactive urinary Bladder disease
   - Tt nocturnal enuresis التبول الليلي
   - urinary inconturince التبول اللاإرادي
   - Flavoxate - oxybutynin → as Transdermal
   - Impipramine → TCA Tricyclic Antidepressant c̄ antimuscuranic effect

3. GIT →
   - AntiSpasmodic (ureter - uterus - biliary tract)
     → Hyoscine - N-butyl bromide - propantheline clidinium - oxyphenonium - Isopropamide } 4ry Amines has no effect on C.N.S
   - anti diarrhea - and in irritable bowel
     → Flavoxate - oxybutynine
   - Tt of Peptic ulcer
     → pirenzepine (selective M_1 Blocker)

4. Eye → To produce mydriasis and cycloplegia
   But Homatropine - Cyclopentolate and Tropicamide are prefered Than Atropine & scopolamine as have low duratn of Actn

5. CNS
   - → Tt of parkinsonism Antipsychotic (D blockers)
     eg Benztropine - Biperide - Tri Hexyphenidyl (3ry amines)
   - → Tt of motion sickness scopolamine → BBB
   - → Anesthesia → ↓ Salivary - bronchial secrtn
     Atropine

6. Cholinergic Poisoning
   Effect of organophosphates - Atropine 1-2mg I.V every 5-15 mins until signs Appear (Dry mouth. miosis)

(d) Therapeutic Uses:

ممكن استخدمها للآتي:

1. Bronchial asthma
2. Urinary tract diseases
3. GIT
4. Eye.
5. CNS
6. cholinergic poisoning.

تعالوا نتكلم عن واحدة بالتفصيل

1. Bronchial asthma, COPD: (Chronic Obstructive Pulmonary disease)

* Ipratropium (administered by inhalation) → donot produce adverse effects on mucociliary clearance as does atropine.
  وده لأنه 4ry فمش هيحصله absorption فمتقللك
  الـ adverse effects بتاعت الـ atropine.
  يبقى الـ atropine
  → more potent but non selective.

* Antihistaminics in "cold" mixtures are due primarily to their antimuscarinic properties.
  بيستخدموهم في ادوية البرد علشان بيوسع الشعب الهوائية فيخف.

2. Overactive Urinary (bladder) disease : , nocturnal enuresis تبول ليلى , urinary incontinence التبول اللا ارادى

انا عايز اقلل الـ urination يبقى اقلل الـ parasymp. effect يعنى يبقى هاستخدم الـ parasympatholytics زى :

* Flavoxate , Oxybutynin → as transdermal , shows lower incidence of side effects (dry mouth & eyes that limit tolerability c̄ continued use)

* Imipramine (TCA = tricyclic antidepressants with Antimuscarinic action)
يعنى هو دواء للاكتئاب بس له 2ry effect انه له antimuscarinic action فيستخدمو للـ "nocturnal enuresis"

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3. GIT :

1) Antispasmodic (biliary tract, ureter & uterus) → use Hyoscine, N-butylbromide, Propantheline, Clidinium, Oxyphenonium, Isopropamide (4ry amines, that are less absorbed & has no central effect)

2) Irritable bowel, Antidiarrhoeal, Excessive salivation :

use Dicyclomine, Flavoxate, Oxybutynin.

3) Peptic Ulcer ⟶ Pirenzepine ⟶ has relative selectivity for M_1 receptors and limited penetration into the CNS.

4- Eye:

To produce Mydriasis & cycloplegia (loss of accomodation for near vision) ⟶ Homatropine, Cyclopentolate & Tropicamide are preferred ill topical atropine or Scopolamine, due to their shorter duration of action

علشان زى ما قلنا ان ال atropine بيقعد لفترة طويلة (72 hrs)
فياخده المريض ويفضل يعانى منه مدة ، لكن الادوية دى
قصيرة فأحسن.

5- CNS:

1) For Parkinsonism, extrapyrimidal side effects of antipsychotics (D blockers)

ال antipsychotics دى بتقفل ال D receptors او ال Dopaminergic receptors

اللى هى عكس ال cholinergic receptors . طب انا هنا لازم استخدم
3ry cpds علشان انا عايزة التأثير فى ال CNS.

use: Benztropine, Biperiden & Trihexyphenidyl ⟶ 3ry amines that gain access to the CNS

2) For motion sickness → Scopolamine (pass bbb) [3ry ↓]
وقاي ← (prophylactically & transdermal)

3) For Anesthesia التخدير → Atropine (premedication to block responses to vagal reflexes induced by surgery or neostigmine & to reduce salivary and bronchial secretions during the surgery)

لازم اقلل ال secretions دي لأن اثناء العملية علشان ممكن تقل blocking لل airway فممكن يتخنق.

6- Cholinergic poisoning:

as CNS, peripheral effects of organophosphates (cholinomimetics)

→ ttt: Atropine sulfate → given as: (dose)

- 1-2 mg IV every 5-15 mins until signs of effect appear (dry mouth, reversal of miosis)
- as much as 1 g/day may be required for as long as 1 month for full control of muscarinic excess.

خلصنا كده ال therapeutic uses
فاضلنا كده ٣ مواضيع بس صغيرين:

e- Adverse effects
f- contraindications
g- Interactions

ADverse Effect

1. Sandy eye
2. Blurred vision
3. Dry mouth
4. Tachy cardia
5. Constipatn
6. Hot and flushed skin

→ CNS

1. Drowsiness
2. Confusion
3. Hallucinatn
4. Delirium → Followed by depression respiratory faliure → Coma.

(e) Adverse effects :

اغلبها حاجات قلناها في النص واحنا ماشيين

1. dry mouth
2. blurred vision زغللة
3. "Sandy eyes"
4. hot and flushed skin
5. tachycardia
6. Constipation

central effects as :

7. Restlessness
8. confusion
9. hallucinations
10. delirium (معنديش فكرة)

هذيان

↓

may progress to depression, collapse of the circulatory & respiratory systems ⟶ death

وعلشان نسهل الحفظ فيه جملة كده توصف الانسان اللى عنده adverse effects دى :

dry as a bone (1), blind as a bat (2, 3) خفاش, red as a beet (4) بنجر, mad as a hatter (7 → 10)

رجل معتوه او مجنون

* Contra indicatn *

1- Glucoma
2- Prostatic enlargement
3- fever
4- Tachy Cardia

* interACTn *

[1] Antimucarinic + Drugs have antimuscarinic
↓ ↑ Anti mucarinic effect

Anti Histaminic
Anti Depressant → Tricyclic
Anti Psychotic → phenoThiazine

[2] Antimuscarinic + MAOIs
↓ ↑ Antimuscarinic effect

[3] Antimuscarinic + Parasympathomimetic
↓
Counteract each other

[4] Antimuscarinic (↓ gastric sec.) affect
↓ absorptn of other Drugs.

(f) Contraindications - Precautions :

1- Glaucoma لاننا قلنا انه هيزود ال IOP أوى

2- Prostatic enlargment (urinary retention)

• علشان اصلاً ال prostatic enlagment بيخلى عملية ال urination صعبة فما ينفعش ادليه كمان ال cholinolytics دول اللى كمان بيقللوا ال urination .

3- Paralytic ileus
4- Fever
5- Tachy cardia

لانه هو بيسبب الحاجات دى فلو المريض عنده اصلاً دول ، لو اخد الادوية دى ← هيزيدوا أوى ← خطر .

وآخر عنوان فى ال antimuscarinic agents :

(g) Interactions :

1- The effects of atropine & other antimuscarinics may be enhanced by the concomitant use of other drugs with antimuscarinic properties, such as:
some antihistamines, phenothiazine antipsychotics & tricyclic antidepressants.

قلنا الكلام ده قبل كده .

2- MAOIs (Monoamine oxidase inhibitors) may enhance the effects of antimuscarinics

3- The reduction in gastric motility caused by antimuscarinics may affect the absorption of other drugs.

4- Antimuscarinics & parasympathomimetics may counteract each other effects → طبيعى يعنى .

طب احنا كده خلصنا اول نوع من ال antagonists اللى هو ال antimuscarinic وعرفنا عنا كل حاجة تقريباً وعرفنا ان ده اهم gp. تعالوا نشوف تانى gp. وهو :

II Antinicotinic drugs

ودول نوعين

Neuromuscular blockers

ده بيشتغل على ال neuromuscular junction.

اللى بين ال nerve ending وال receptor اللى على ال muscle

وبالتالى دول more selective عن التانيين وبيستخدموا اكتر شوية

Ganglionic blockers

ده بيشتغل على ال ganglia

يعنى ال junction اللى بين ال nerves ع مالوش دعوة بالمنطقة اللى بين ال nerve وال muscle

وبالتالى هو nonselective مش هيفرق بين sympathatic or parasymp. ganglia

هيأثر على الاتنين وبالتالى مش بيستخدم كتير.

كده فكرة عامة عن الاتنين ، يلا نشوف واحد واحد كده بالتفصيل شوية ... ...

AntiNicotinic Drugs

Ganglionic Blocker

- Nn
- Non Selective < Symp. / Para-Symp.
- Ion Channel Coupled R.

e.g **1 Nicotine**

Dil
- Stimulatory effect is complexed < sy / par.
- ↑ B.P
- ↑ secretn
- ↑ Heart Rate

as it stimulate the ganglionic To produce Epinephren - N-E

Conc.
- ↓ B.P
- ↓ Heart Rate
- ↓ GIT Activity. Bladder

2 Trimethaphane
- Short duratn
- I.V infusion
- Competetive Nicotinic ganglionic Blocker

3 Mecamylamine
- long duratn
- orally (Adv)
- Competetive Blocker

Neuromuscular Junctn Blocker

Nm → skeletal M.

Drugs

Central muscle Relaxant

↓

e.g
- Diazepam → binds ē GABA
- Dantrolene → Directly Acting on muscle interfer ē Ca^{++} release
- baclofen → Act on GABA

Ach analogue

Competetive Nm Blocker

Antagonist

Non Depolarizing

↓

bind ē R and Block it

↓ no Actn

relaxatn

Non Comp. Nm Blocker

Agonist

Depolarizing

↓

bind ē R and give the same Actn of Ach at the first

↓

Contratn but not Breaked down So

↓

relaxatn

e.g Succinylcholine

(1) Ganglionic Blockers

* Ganglionic blockers specially act on the nicotinic receptors, probably by blocking the ion channels of the autonomic ganglia (N_N receptors) → المحاضرة الثالثة

* These drugs show no selectivity towards the parasympathetic or sympathetic ganglia & not effective as neuromuscular antagonists

∴ the responses observed are complex and unpredictable, making it impossible to achieve selective actions
نفس الكلام اللى قلناه الصفحة اللى فاتت

∴ Ganglionic blockers are rarely used therapeutically today. However, they often serve as tools in experimental pharmacology.

⊛ طيب تعالوا نشوف ٢ امثلة لادوية بيشتغلوا بال mechanism ده
ومش هنتكلم فيهم كتير ...

(A) * Nicotine *

* A component of cigarette smoke, Nicotine has many undesirable actions.
* Depending on the dose, nicotine depolarizes ganglia, resulting 1st in stimulation followed by paralysis of all ganglia.

i.e ⊛ at low dose (dil nicotine) → stimulation.
↓
stimulatory effects are complex — علشان شغالة على السوتين sympathatic + parasymp.

includes : 1- ↑ in blood pressure & cardiac rate →

طب ليه ؟!
علشان هو بيشتغل على الـ ganglia فتحت الـ adrenal gland ، هيطلع الـ norepinephrine , epinephrine
اللي هيشتغلوا على الـ sympathatic في القلب مثلاً ويعملوا ↑B.P & ↑ cardiac rate.

2- ↑ peristalasis & secretions
لما يزود الـ parasymp. effect

⊛ at higher doses (conc. nicotine) → paralysis of all ganglia.

causes : 1 fall in blood pressure due to ganglionic blockade.

2 Activity both in the GIT & bladder musculature ceases تقف

وده طبعاً لأن قفلت الـ ganglionic receptors فـ impulses مش هتوصل اصلاً للـ neuromuscular junct^n سواء symp. or parasymp فمش هيحصل اى effect.

(B) * Trimethaphan *

* It is short acting, competitive nicotinic ganglionic blocker that must be given by IV infusion.

يعني لو اديت dose اكبر من ال agonist هيشيله ويقعد مكانه

* Today, the drug is used for the emergency lowering of blood pressure when other agents cannot be used.

(C) * Mecamylamine *

زي اللي فوق

* produces a competitive nicotinic block of the ganglia
* long duration of action (10 hrs)
* The uptake of the drug via oral absorption is good in contrast to trimethaphan.

⊛ المهم تعرفه عنه انه : active orally & long duration of action

بس كده خلصنا ال ganglionic blockers

يلا نشوف تاني نوع

(2) Neuromuscular Blocking drugs

* These are drugs that block the cholinergic transmission between motor nerve endings & the nicotinic receptors on the neuromuscular end plate of skeletal muscle.

نفس الكلام اللى قلناه فى التقسيمة اللى عملناها من شوية

* النوع ده من ال blockers عبارة عن structural anologues of Ach
يعنى علشان يعرف يمسك فى ال receptors بتاعت ال Ach لازم يكون شكله شبهه ، طب بعد ما يمسك !؟ ممكن يشتغل بطريقة من اتنين :

(1) يا إما antagonist او nondepolarizing وده اللى احنا عارفينه العادى يعنى ، اللى هيمسك فى ال receptors ويمنع انه يحصله depolarization وبكده يبقى قفله وده تأثيره هيبان على طول على هيئة مثلاً فى ال relaxation muscles.

(2) النوع التانى بقى يبقى agonist او depolarizing
طب ازاى هيعمل blocking !؟ هو هيمسك الاول فى ال receptor وهيعمل تأثير زى ال Ach يعنى مثلاً contraction ، طب وبعدين !؟
الطبيعى فى ال Ach العادى انه بعد ما يعمل كده ، يتفك ويتكسر بال acetyl cholinesterase
لكن هنا مش هيحصل كده ، الدواء ده هيفضل لازق فى ال receptor ومش هيسيبه فنجد شوية ال receptor هيتعب ويبطل يبعت impulses وبالتالى هيحصله زى paralysis وال muscle يحصل relaxation
زى ايه احنا !؟ ال succinyl choline او ال suxamethanioum.
فهمتوا كده !؟

لو فهمتوا الكلام كلمة اللى فوق ، يبقى الجزء الجاى ده هيبقى حلو أوى ان شاء الله ....

* These neuromuscular blockers are structural analogs of acetyl choline & act either as - antagonists (non depolarizing type) or agonists (depolarizing agonist) at the receptors on the endplate of the neuromuscular junction.

* Neuromuscular blockers are clinically useful during surgery to produce complete muscle relaxation without having to use higher anaethetic doses to achieve comparable muscular relaxation.

فيه نوع تاني من ال muscle relaxants غير اللي يكون st. analog of Ach
↓

* A second gp of muscle relaxants, the central muscle relaxants → used to control spastic muscle tone.
These drugs include:
  1) diazepam (binds to GABA receptors)
     الدكتور مشرحهاش عشان احنا اخدناها في الفارما، اللي عايز يفهمها يرجع للفارما او يجيب نشرحهاله علشان ما نطولش هنا

  2) Dantrolene → acts directly on muscles by interfering with release of Ca from the Sarcoplasmic reticulum.

  3) baclofen → probably act on GABA receptors in the CNS.

نشوف الموضوع بقى ← هنتكلم عن :
1- Non depolarizing (competitive) blockers.
2- Depolarizing (Non competitive)

* Non Depolarizing Nm Blocker
* Competitive Nm Blocker

[1] e.g Curare and Tubocurarine Alkaloids

[2] MoA → AT ↓ low dose → Block Nm R → ↓ muscle Contractn
This Actn overcomed by ↑ Ach (by Cholinesterase inhibitor (physostigmine . Edrophonium))
→ AT ↑ dose → Block Nm R and also block Ion channel on ↓ end plate So ↓ Ability of Cholinesterase inhibitor Drugs To reverse ↓ effect of Competitive Blocker ↓

[3] Actions

rapidly appear on Small muscles of face and eye → fingers → neck, limb, Trunk → intercostal muscle (last) → Diaphragm (paralysis)

[4] Therapeutical uses
ē anesthesia To ↓ Dose of it during surgery

[5] pharmaco kinetics . neuromuscular Blocker Taken only I.V ??
as ↓ absorptn orally is minimized
- poorly penetrate cell membrane & BBB
- most Drugs excreted unchanged (no metabolism)
  eg Tubocurarine - Pancuronium - mivacurium - doxacurium
- Atracurium Degraded spontaneously in plasma by ester hydrolysis
- Vencuronium - rocuronium → Deacetylated in liver
  So Their clearance are prolonged ē patient ē hepatic disease

[6] Adverse Effect . Tubocurarine → ↑ Histamine release
(broncho spasm - hypotension - ↑ salivary secretn)
. promotes ganglionic Blocker → ↓ BP

[7] Drug interActn . cholinesterase inhibitory ↓ Dose → ↓ Blocking
↑ Dose → ↑ ″

Block Na^+ channel ← . Halogenated hydrocarbon anesthetics
Compete ē Ca^{++} Ion → ↓ Ach ← . Aminoglycoside AntiBiotic (gentamycin, Tobramycin) ↑ ″
↓ Ach ← . Ca Channel Blocker

(A) Non depolarizing (competitive) Blockers :

* هو نفس الكلام اللى قلناه قبل كده لكن نسيت اقولكم انه بيبقى competitive يعنى لو زودت ال Ach هيشيله ويقعد مكانه لكن ال depolarizing ده non competitive يعنى مش هيتأثر بال Ach لانه هو اصلاً طريقة شغله انه بيسيبك لفترة طويلة فى ال receptor علشان يشله ، لكن لو كان competitive يبقى لو زودت الـ Ach ، ابقى بوظته ومش هيدى التأثير اللى مستنياه منه

* تعالوا نكتب الكلمتين دول ... بس الاول نشوف حتة كده دراسات اجتماعية عن اكتشاف الادوية دى ...

* The 1st drug that was found capable of blocking the skeletal neuromuscular junction was (1) "Curare"

which was used by the native hunters of the Amazon in South America to paralyze animals.

كانوا بيحطوه فى السهام اللى بيصطادوا بيها الحيوانات

(2) "Tubocurarine" was ultimately purified and introduced into clinical practice.

* The neuromuscular blockers have significantly ↑ the safety of anaethesia, since less anaethesia is required to produce muscle relaxation.

يعنى الاول كانوا بيدوا جرعة كبيرة من التخدير علشان يعمل muscle relaxation قبل العمليات ، لكن له مخاطره. لكن بعد ما اكتشفوا الـ neuromuscular blockers اللى بتعمل relaxation بره ، بقوا بيستخدموها مع ال anaethesia وبالتالى تقللوا الجرعة اللى محتاجنها للتخدير.

a_ MOA :

1- at low doses :

* Nondepolarizing neuromuscular blockers combine with the nicotinic receptor & prevent the binding of Ach → ∴ prevent depolarization of the muscle cell membrane & ↓ muscular contraction.

وده الكلام اللي قلناه قبل كده، انه بيجي يمسك مكان الـ Ach على الـ receptor وبالتالي مفيش depolarization ← يبقى مفيش contraction

* Because these agents compete with Ach at the receptor → they are called "Competitive blockers"

This action can be overcomed by increasing the conc of Ach in the synaptic gap, for example by administration of cholinesterase inhibitors (∴ ↑ Ach) such as : neostigmine, or edrophonium.

دكاترة التخدير

↳ Anaesthesiologists often employ this strategy to shorten the duration of the neuromuscular blockade

يعني احنا قلنا انه بيستخدم كـ muscle relaxant في العمليات الجراحية علشان اقلل الـ dose بتاع الـ anethetic، طب العملية خلصت، عايزة افك الـ blockers دي بقى علشان يقدر يعمل contraction تاني ← اديله cholinesterase inhibitor ← يزود الـ Ach ← يشيل الـ blockers ويمسك مكانها ← يعمل contraction

طب ده في الـ low dose ← كل اللي هيحصل انه هيشغل الـ receptor ← طب لو زودت الـ dose. هيحصل ايه؟!

2. At High doses:

* Non depolarizing blockers block the ion channels of the end plate → this leads to further weakening of neuromuscular transmission & reduces the ability of acetylcholinesterase inhibitors to reverse the action of non depolarizing muscle relaxants

يعني ايه ؟!

يعني لو زودت الـ dose بتاعت الـ NM blockers دول ←
يعني انه قفل الـ receptor ومنع الـ Ach انه يمسك فيها ، لا ده
كمان هيقفل الـ ion channels اللي موجودة على الـ endplate بتاعت
الـ muscle ← طب ممكن حد يسأل: وهو الـ ion channels ايه فايدتها
اصلاً مادام الـ blockers دي قافلة الـ receptors ؟
• هنقول انه ده competitive ، يعني لو زودت الـ Ach* هيشيل
الـ blockers من الـ receptors ويمسك مكانها ، بس مفروض بعد كده
انه يبين الـ effect بتاعه عن طريق الـ ion channels علشان يحصل depolarization
ويحصل contraction ← لكن هنا حتى الـ channels دي مقفولة
← no depolarization ← no contraction

* عن طريق الـ cholinesterase inhibitors

---

b- Actions:

اسرع عضلات هتشتغل عليها وبان عليها التأثير

↓

1. Small, rapidly contracting muscles of the face and eye are most susceptible & are paralyzed 1st

   ↓

   followed by

2. the fingers.

↓

③ limbs, neck & trunk muscles.

↓

④ the intercostal muscles are affected

↓

and lastly,

⑤ the diaphragm muscles are paralyzed

---

c. Therapeutic uses:

* These blockers are used as adjuvant drugs in anesthesia during surgery to relax skeletal muscle

• وعرفنا ان ده علشان اقلل ال dose بتاعت المخدر اللى ممكن يعمل toxicity لو زاد، اتفادى ده بانى ادى معاه ال blockers اللى هتعمل معاه relaxation.

---

d. Pharmacokinetics:

نعرف ايه اخبار ال absorption وال metabolism وال excretion بتاعت الادوية دى؟!

* All neuromuscular blocking agents are injected intravenously, why?!

because their uptake via oral absorption is minimal.

* they penetrate membranes very poorly and donot enter cells or cross the bbb

* Many of these drugs are not metabolized → their actions are terminated by redistribution.
For example,
tubocurarine, pancuronium, mivacurium & doxacurium are excreted in the urine unchanged.

* Atracurium is degraded spontaneously in the plasma & by ester hydrolysis.

* The aminosteroid drugs as: Vencuronium & rocuronium → are deacetylated in the liver → and their clearance may be prolonged in patients with hepatic diseases
These drugs are also excreted unchanged in the bile (i.e. through feces)

---

e- Adverse effects:

* d-tubocurarine may induce histamine release (eg: bronchospasm, hypotension, excessive bronchial and salivary secretion) as a direct action on the mast cell rather than IgE mediated anaphylaxis.

* The drug can also promote ganglionic blockade & lower blood pressure

يعني ايه ؟!

احنا قلنا انها بتقفل الـ nicotinic receptors اللى عند الـ neuromuscular junction

لكن لما الـ dose بتزيد ← الـ selectivity بتقل فممكن تقفل كمان الـ nicotinic receptors (N_N) اللى فى الـ ganglia

← الـ sympathatic مثلاً عند القلب ← لما اقفل الـ ganglionic receptor

← هيقلل الـ blood pressure

E Drug Interactions :

طبعي ان اى حاجة بتساعد على زيادة الـ Ach ← تبقى هتعاكس التأثير بتاعهم وأى حاجة تقلل الـ Ach او تساعد على قفل الـ ion channels

يبقى هتساعدهم وتزود تأثيرهم.

1) Cholinesterase inhibitors : drugs such as neostigmine, physostigmine and edrophonium → ↑ Ach

∴ can overcome the action of nondepolarizing neuromuscular blockers but with elevated dosage but, cholinesterase inhibitors can cause a depolarizing block as a result of elevated Ach conc. at the end plate membrane.

يعني ما اقولش اى ادليه chol. inhibitors كتير علشان تشيل كويس الـ blockers من على الـ receptors ← لانها هتزيد اوى الـ Ach ← صحيح هتشيل الـ blocker لكن الـ Ach كده هو اللى هيعمل blocking

2) Halogenated hydrocarbon anethetics: drugs such as halothane act to enhance neuromuscular blockade by exerting a stabilizing action at the neuro muscular junction

ازاي ؟!

الـ anethetics دول بيقفلوا الـ Na channels وبالتالي بيزودوا تأثير الـ NM blocking

3) Aminoglycoside antibiotics: drugs like gentamicin or tobramycin → ↓ acetylcholine release from cholinergic nerves by competing with Ca ions.
∴ they synergize with tubocurarine and other competitive blockers, enhancing the blockade.

احنا عارفين ان الـ Ca^{+2} بييجي على الـ vesicles اللي مخزنة الـ Ach ويخليها تطلعه ← الـ antibiotics دي بتعمل competition مع الـ Ca^{+2} وبالتالي بتقلل طلوع الـ Ach ← ↓ Ach ← يبقى بتزود تأثير الـ blockers.

4) Ca channel blockers: these agents may ↑ the neuromuscular block of tubocurarine & other competitive blockers as well as depolarizing blockers.

يبقى:

1) cholinesterase inhibitors: low dose → ↓ blocking
high dose → ↑ blocking but by Ach.

2) Halogenated hydrocarbon anethetics
3) aminoglycoside antibiotics
4) Ca channel blockers

} ↑ blockade effect

طب تعالوا نشوف تاني نوع من ال blockers ، اللي هو :

(B) Depolarizing (Non competitive) agents : Agonist

⊛ الفرق بينه وبين اللي فات ان ① اللي فات كان antagonist يعني عكس شغل ال Ach لكن ده اصلاً agonist يعني اول ما يمسك بيدي نفس التأثير بتاع ال Ach.

② اللي فات كان competitive يعني هزود ال Ach هيشيله من على ال receptor ، لكن ده non competitive يعني مهما زودت ال Ach ← مش هيأثر.

③ اللي فات كان nondepolarizing يعني بيمنع ال depolarization ، لكن ده depolarizing ، عامل زى ال Ach اول ما يمسك بيعمل depolarization ويعمل contraction لكن مش هيتكسر بال acetylcholinesterase زى ال Ach ← فكتر ال depolarization هتعمل paralysis في ال muscle.

⊙ احنا مش هناخد فيه غير مثل واحد وهو ال : Succinyl choline or Suxamethonium.

a. Mechanism of action : مش هنقول فيه حاجة جديدة

* The depolarizing neuromuscular blocking drug, succinyl choline → attaches to the nicotinic receptor and acts like Ach to depolarize the junction but, unlike Ach which is instantly destroyed by acetylcholinesterase, the depolarizing agent persists at high conc. in the synaptic cleft → remaining attached

* Depolarizing Nm Blocker *

* Non Competitive Nm Blocker *

1. e.g Succinyl Choline - Suxamethonium
2. MOA
   - Binds ē NmR and give the same Actn of Ach at the first but not hydrolysed by Cholinesterase so due to Continuous Contractn → Paralysis
   - once binding → Depolarizatn (Na-Channel opening)

phase I → Transient Twitching of muscle → gradually To Paralysis

Phase II → Spastic Paralysis (due To ↑ Contractn)

3. Actn
   - respiratory muscle are Paralyzed last like Competitive
   - Succinyl Choline have short duratn of Actn why?? As rapidly Brocken by Plasma Cholinesterase
   - Dosent lead To ganglionic Blocker even ē ↑ Dose
   - have weak Histamine release
4. Therapeutic use
   - used when endotrachial intubatn is required → as it have rapid onset and short duratn of Actn To avoid aspiratn of gastric Content during intubatn
5. pharmacokinetics
   - Succinyl Choline → I.V infusion rapidly hydrolysed by Plasma Cholinesterase
6. Adverse effect
   - Apnea توقف التنفس due To defficiency in plasma esteras → diaphragm Paralysis
   - Hyper Thermia

to the receptor for relatively long time & providing a constant stimulation of the receptor.

⊛ The depolarizing agent 1st causes the opening of the Na channel associated with the nicotinic receptors, which results in the depolarization of the receptor.
→ Phase (I) → these leads to transcent twitching of the muscle (Fasiculations) رعشة
(contraction يعني)

phase I دي العاملة الجزء اللي شبه ال Ach. ...

↓

The continued binding of the depolarizing agent renders the receptor incapable of transmitting further impulses giving way to gradual paralysis
→ Phase (II)

Spastic paralysis واحنا قلنا ان نوع الشلل ده اسمه
يعني شلل من كتر ال spasm او ال contraction.

---

b- Actions:

* The sequence of paralysis may be slightly different, but as seen with the competitive blockers, the respiratory muscles are paralyzed last.

* Succinyl choline initially produce short lasting muscle fasiculations, followed with few mins by paralysis

* The drug doesnot produce a ganglionic block, except in high doses, although it does have weak histamine releasing action.

* Normally, the duration of action of succinyl choline is extremely short, since this drug is rapidly broken down by plasma cholinesterase.

احنا قلنا انه مش بيتكسر بال acetylcholinesterase لانه خصوصي لل acetyl ch. لكن
بيتكسر بال cholinesterase اللي في ال plasma.

C- Therapeutic uses:

* Because of its rapid onset & short duration of action → succinyl choline is useful when rapid endotracheal intubation is required during the induction of anethesia &

يعني ساعات مع التخدير ، باحتاج ادخل ال tube في ال trachae
علشان التنفس ← فاكون محتاج حاجة تعمل paralysis سريعة
بس لمدة قصيرة ← ده اللي بيعمله ال succinyl choline
طب ليه محتاجاه يكون لمدة قصيرة ؟!

to avoid aspiration of gastric contents during intubation
يعني انا بشل العضلات فممكن ال gastric contents تجي من ال sphincters
فعلشان كده عايز حاجة سريعة .

* It is also employed during electroconvulsive shock treatment
مش عارفة يعني ايه .

d- Pharmacokinetics:

Succinyl choline is injected intravenously, its brief duration of action (several mins) results from rapid hydrolysis by plasma cholinesterase

∞ It is usually given by continous infusion.

e- Adverse effects:

1- Apnea: توقف التنفس

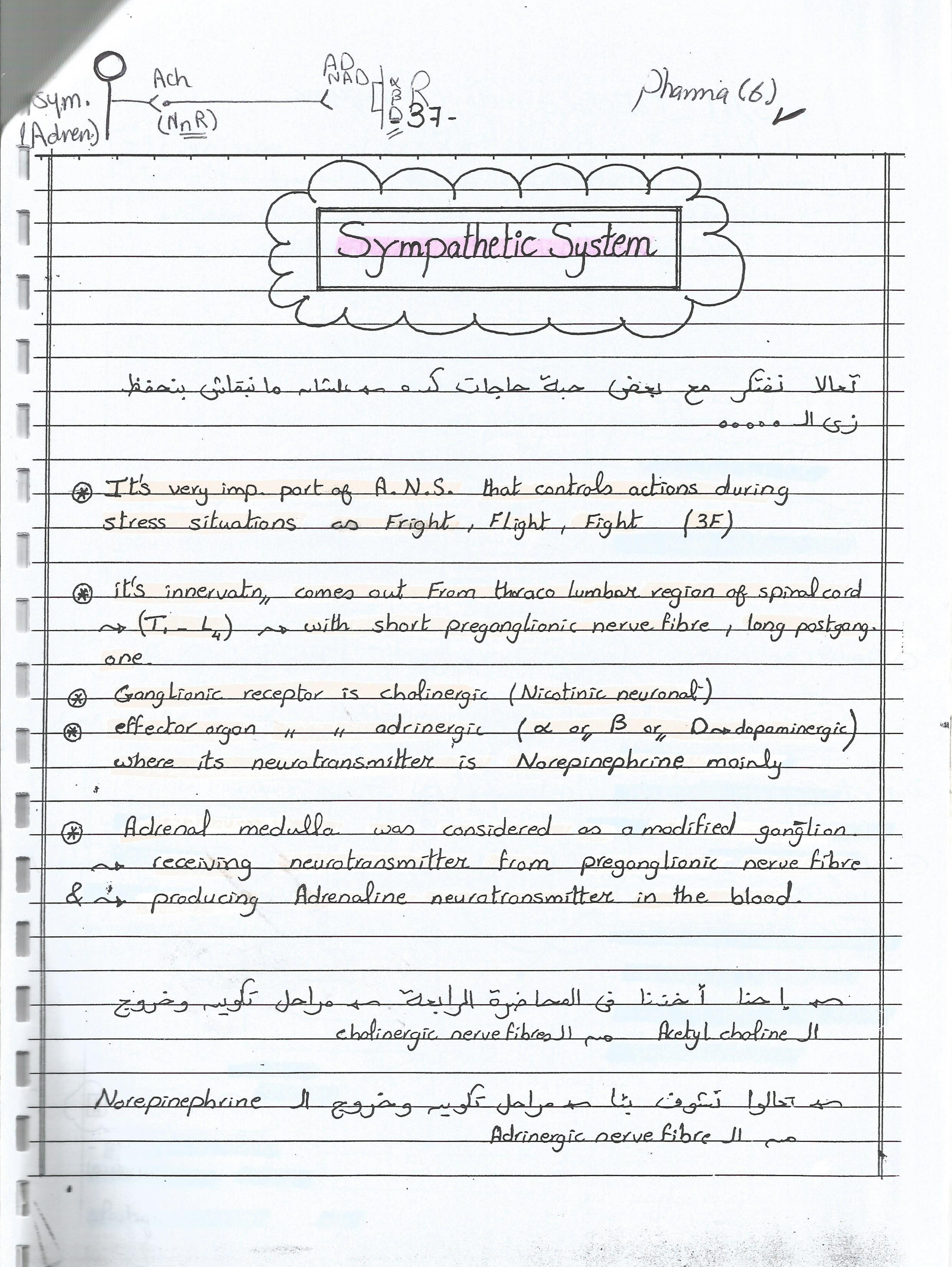
A genetically related deficiency of plasma cholinesterase or presence of an atypical form of the enzyme can lead to apnea due to paralysis of diaphragm.

2- Hyperthermia: ارتفاع درجة الحرارة

When halothane is used as an anesthetic, administration of succinyl choline has occasionally caused malignant hyperthermia (with muscular rigidity and hyperpyrexia) in genetically susceptible people.

→ ألف مبروك → كده إحنا خلصنا الـ Parasympathetic system
بكل ما فيه → Agonists, antagonist

→ افضل شوية بنا → علشان هنبتدى فى الـ Sympathetic system.
→ نصيحة → افضل الـ Parasym. كله عن الـ Symp.
وذاكر مواضيع → مش محاضرات → علشان متتلخبطش
يعنى أفضل إنك تفصل الجزء القادم عن المحاضرة وتعتبره محاضرة جديدة.



Sym. (Adren.) — Ach (NnR) — AD NAD — α β D R

37-

Pharma (6)

Sympathetic System

تعالا نفتكر مع بعض حبة حاجات كده علشان ما نبقاش بنحفظ زي الـ .....

- It's very imp. part of A.N.S. that controls actions during stress situations as Fright, Flight, Fight (3F)

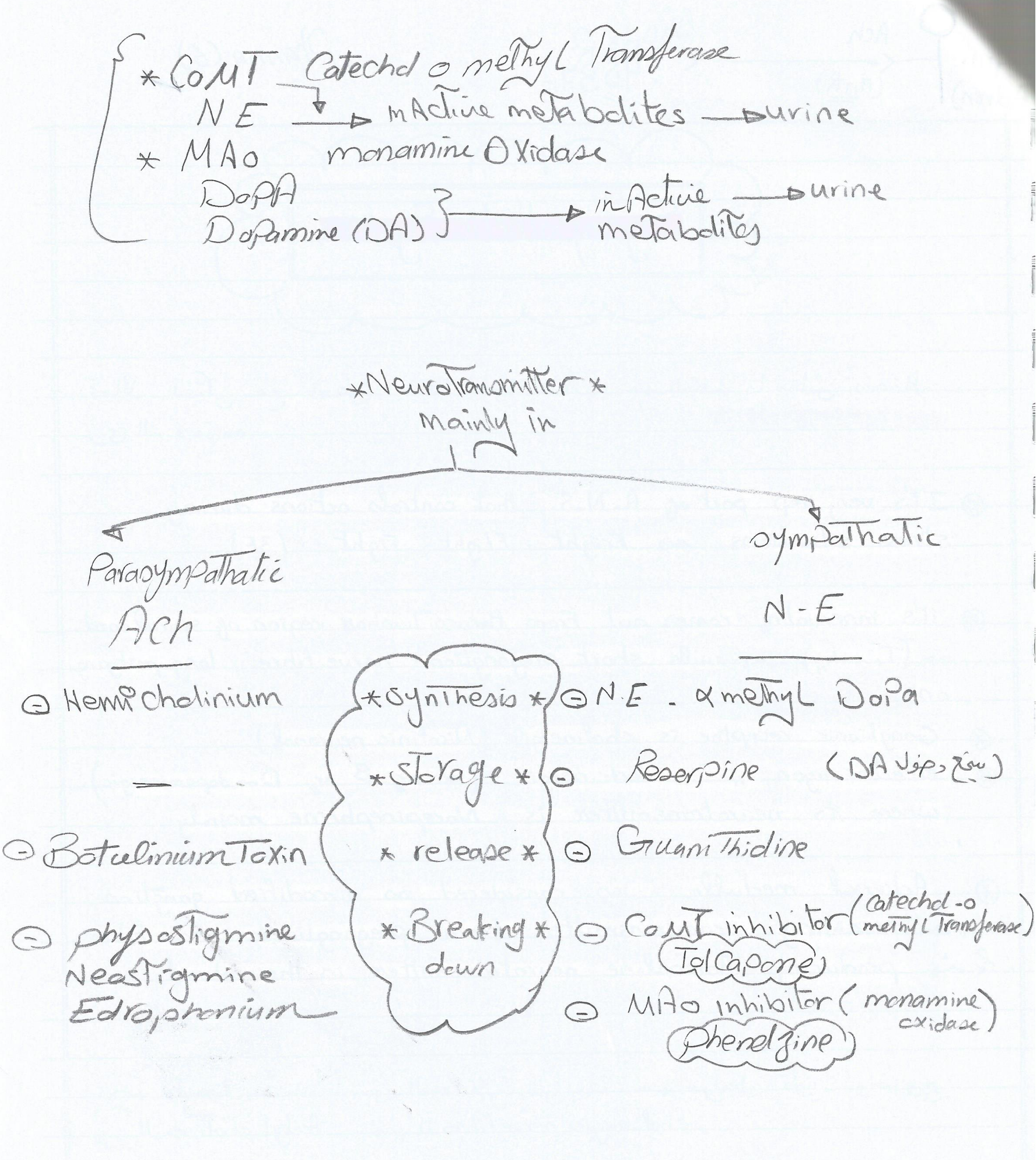
- it's innervatn. comes out from thraco lumbar region of spinal cord → ($T_1 - L_4$) → with short preganglionic nerve fibre, long postgang. one.

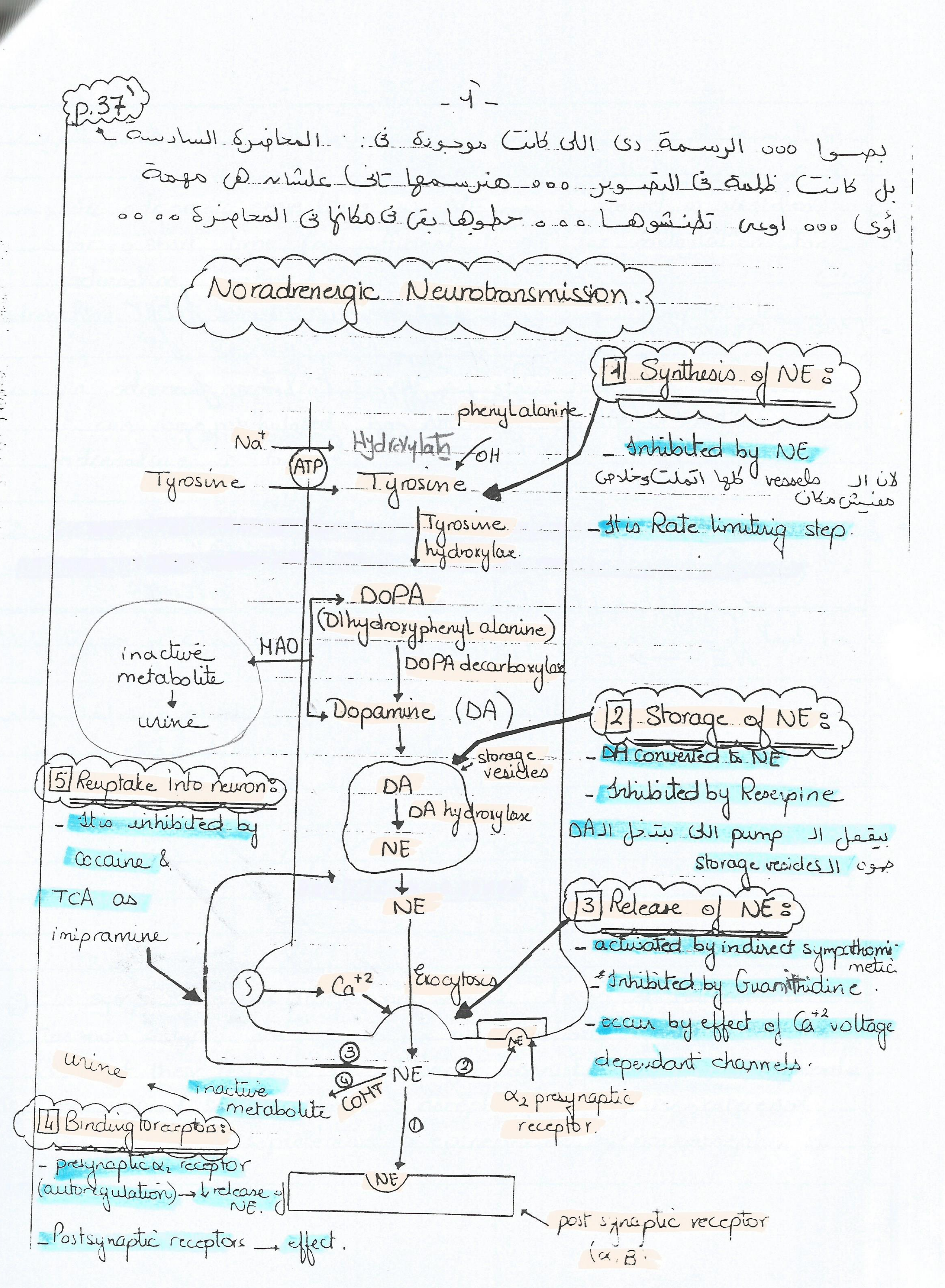
- Ganglionic receptor is cholinergic (Nicotinic neuronal)
- effector organ " " adrinergic (α or β or D → dopaminergic) where its neurotransmitter is Norepinephrine mainly

- Adrenal medulla was considered as a modified ganglion.
  → receiving neurotransmitter from preganglionic nerve fibre
  & → producing Adrenaline neurotransmitter in the blood.

← إحنا أخدنا في المحاضرة الرابعة ← مراحل تكوين وخروج الـ Acetyl choline ← من الـ cholinergic nerve fibres

← تعالوا نشوف بقا ← مراحل تكوين وخروج الـ Norepinephrine ← من الـ Adrinergic nerve fibre


* COMT Catechol o methyl Transferase
NE → inActive metabolites → urine
* MAo monamine Oxidase
DoPA
Dopamine (DA) → inActive metabolites → urine
NeuroTransmitter
mainly in
Parasympathatic
sympathatic
Ach
N - E
⊖ Hemicholinium
synthesis
⊖ N.E . α methyl Dopa
storage
⊖ Reserpine (يمنع دخول DA)
⊖ Botulinium Toxin
release
⊖ GuaniThidine
⊖ physostigmine
Neastigmine
Edrophonium
Breaking down
⊖ COMT inhibitor (Catechol-o methyl Transferase)
Tolcapone
⊖ MAo inhibitor (monamine oxidase)
Phenelzine


p.37
- ٦ -
بصوا ... الرسمة دى اللى كانت موجودة فى : المحاضرة السادسة
بل كانت ظلمة فى التصوير ... هنرسمها تانى علشان هى مهمة
أوى ... اوعى تكنشوها ... حطوها بقى فى مكانها فى المحاضرة ....
Noradrenergic Neurotransmission.
1 Synthesis of NE:
- Inhibited by NE
لان ال vessels كلها اتملت وخلاص مفيش مكان
- It is Rate limiting step.
phenylalanine
Hydroxylation
OH
Na+
ATP
Tyrosine
Tyrosine
Tyrosine hydroxylase
DOPA
(Dihydroxyphenyl alanine)
DOPA decarboxylase
MAO
inactive metabolite
urine
Dopamine (DA)
2 Storage of NE:
- DA converted to NE
- Inhibited by Reserpine
بيقفل ال pump اللى بتدخل ال DA جوه ال storage vesicles
storage vesicles
DA
DA hydroxylase
NE
5 Reuptake into neuron:
- It is inhibited by Cocaine & TCA as imipramine
NE
3 Release of NE:
- activated by indirect sympathomimetic
- Inhibited by Guanithidine.
- occur by effect of Ca+2 voltage dependant channels.
Exocytosis
S
Ca+2
NE
③
②
④
NE
COMT
①
urine
inactive metabolite
α2 presynaptic receptor.
4 Binding to receptors:
- presynaptic α2 receptor (autoregulation) → ↓ release of NE.
- Postsynaptic receptors → effect.
NE
post synaptic receptor (α, B)

N.B

- the main neurotransmitter in Adrenergic nerve fiber is **N.E** as it stored in vesical for short time so not sufficient time for methylatn of N.E ⟶ Ep. (Adrenaline)

- the main neurotransmitter in Adrenal medulla is **Adrenaline** as it stored in vesical for sufficient time to methylatn occures NE ⟶ E.P [Adrenaline]

⊛ الرسمة اللى فاتت دى ← هى اللى جابها الدكتور بالضبط ← بالحرف

⊛ هو بس زود عليها حاجة واحدة

→ in adrinergic nerve fibre → NE → is stored in vesicles for a short time (not sufficient time) for methylation for adrenaline synthesis.

يعنى الـ NE مش بيلحق يعمله Methylation علشان يتحول للـ adrenaline.

→ in adrenal medulla → NE → stays for along time → So it can be methylated by NE methyl transferase enzyme → adrenaline is formed

∴ the main product of adrinergic nerve fibres is NE. while that of adrenal medulla is adrenaline (epinephrine)

← طبعاً لو مش فاهم أى حاجة فى الرسمة ← إحنا تحت أمر حضرتك يا باشا

← بص يا سيدى ← الكلام اللى جاى لم يقال فى المحاضرة ← إحنا جبناه من الـ Lippincott ← بس بأمانة هيفيدك، محاله لو عرفته ← هتبقى فاهم وهيسهل عليك الحفظ جداً إن شاء الله.

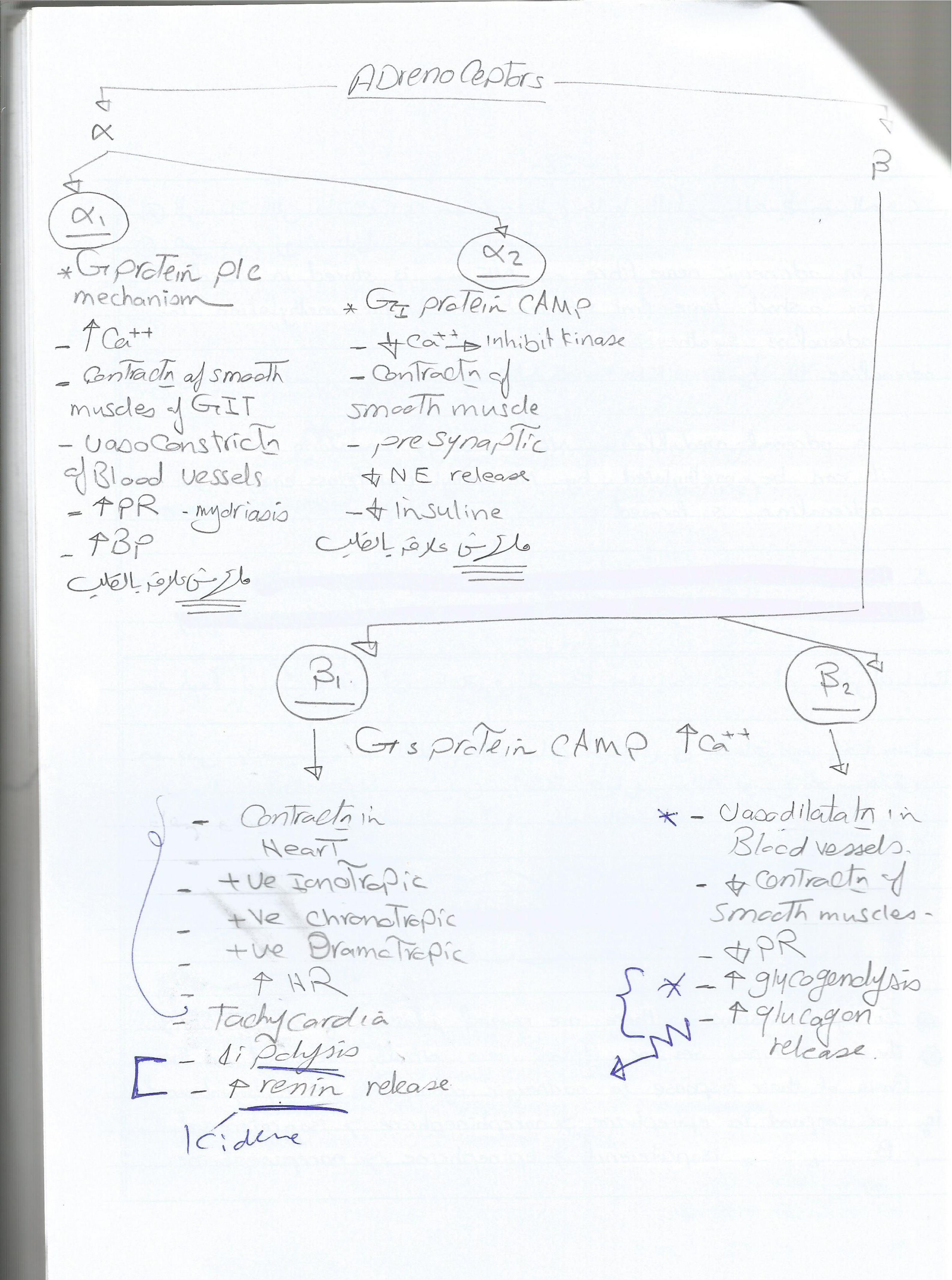
Adrenoceptors

⊛ In symp. system → there are several classes of adrenoceptors

⊛ The main 2 types are α, β → were initially identified on the Basis of their response to adrinergic agonists → NE, E, isoproterenol.

ie, α respond to epinephrine > norephinephrine > isoproterenol.

, β " " isoproterenol > epinephrine > norepinephrine.



ADrenoCeptors
α
β
α1
* G protein plc mechanism
- ↑Ca++
- Contractn of smooth muscles of GIT
- vasoConstrictn of Blood vessels
- ↑PR - mydriasis
- ↑BP
ملوش علاقة بالقلب
α2
* GI protein CAMP
- ↓Ca++ → inhibit kinase
- Contractn of smooth muscle
- presynaptic
↓NE release
- ↓insuline
ملوش علاقة بالقلب
β1
Gs protein CAMP ↑Ca++
- Contractn in Heart
- +ve Ionotropic
- +ve chronotropic
- +ve Dramotropic
- ↑HR
- Tachycardia
- lipolysis
- ↑renin release
Kidene
β2
* - vasodilatatn in Blood vessels.
- ↓Contractn of smooth muscles -
- ↓PR
* - ↑glycogenolysis
- ↑glucagon release.

Adrenoceptors

α

* → respond to epinephrine > norE > isoproterenol

β

* respond to isoproterenol > epinephrine > NE

α

α_1

⊛ works by G protein PLC mechanism

← فاكر ولا ؟

∴ ↑ Ca^{+2} causing smooth muscle contraction

ملوش أي علاقة بالقلب

← له علاقة بال Blood vessels

وال smooth muscles

بتاعت ال GIT والحاجات (د) .

* Vasoconstrictn
* increase peripheral resist.
* increase blood pressure.
* mydriasis → radial Ms.

α_2

⊛ works by G_I protein Adenylyl cyclase mechanism.

∴ ↓ Ca^{+2} in secretory glands. ⊕ المختبر

, ↑ Contractn of smooth muscles

← برضه ملوش علاقة بالقلب.

* inhibitn of NE release by mediating presynaptic inhibitn
ie α_2 receptor is the presynaptic receptor
* ↓ Secretn as ↓ insulin Secretion.

β

β_1 / β_2

→ Both β_1, β_2 work by G_s Protein Adenylyl cyclase mechanism

∴ ↑ Ca^{+2} in Cardiac muscle (β_1) → ↑ contractn.

, ↓ contractn in smooth muscles (β_2) → Blood vessels.

β_1

* Tachycardia
* increased lipolysis
* increased myocardial contractility.
* increased renin release.

β_2

* Vasodilatatn
* slight ↓ in peripheral resistance ⊕ مختبر
* relaxed uterine muscles (smooth)
* increased muscle, liver glycogenolysis.
* increased release of glucagon.

(*) → u have to know that → ↑ Ca^{+2} → muscle → contraction
→ Secretory gland → Secretion.

(*) What's peripheral resistance ? (PR)

Answer → - it's the resistance of the small arterioles to the flow of blood inside it.

- this occurs when those arterioles are constricted.
- PR is the main reason for ↑ blood pressure (hypertension)

∴ β_2 causes vasodilatation → ↓ PR → ↓ Blood pressure.

, α_1 causes vasoconstriction → ↑ PR → ↑ Blood pressure.

الحاجات دي لازم تفهمها كويس جداً ← علشان الـ M.O.A بتاع أدوية الضغط كلها هتلاقي فيها الحاجات دي.

(*) Distribution of receptors :

→ Some organs contains 2 types of receptors But only 1 predominates :

example : blood vessels of skeletal muscles contains :

1. α_1 → if sympathetic impulse received → vasoconstriction
2. β_2 → if " " " → vasodilatation

إيه رأيك ← مين اللي هيسود على التاني ؟
إنت لما تيجي تتخانق ← عضلاتك محتاجة دم كتير ولا قليل ؟
أكيد دم كتير ← يبقى أكيد هيحصل vasodilatation ← يبقى أكيد β_2 هو اللي هيسود على الـ α.

→ Some organs contain only 1 type of receptors as the heart contains only β_1 → sympathetically → ↑ contraction.

(ADrenergic Agonist) (Adrenergic neuro...

Sympathomimetics

Catecholamines

- Derivatives of β phenylethyl amine [ring]-CH_2-CH_2NH_2

* Dopamine: HO, HO-[ring]-$CH_2CH_2NH_2$

* N-E: HO, HO-[ring]-CH(OH)-CH_2NH_2

* E: HO, HO-[ring]-CH(OH)-CH_2-N(H)(CH_3)

* Isoprotrenol: HO, HO-[ring]-CH(OH)-CH_2N(CH_3)(CH_3)

→ rapidly deactivated by
- COMT → Post synaptic
  → gut wall
- MAO → intra neuronally
  → gut wall - liver

→ Parentrally ✓
ineffective orally

→ Highly Polar So not penetrate BBB

→ CH_3 gp in E & Isoprotrenol make them more Potent for β Receptor

Non Catecholamines

* phenyl ephrin: HO-[ring]-CH(OH)-CH_2-N(H)(CH_3)

* Ephedrine: [ring]-CH(OH)-CH(CH_3)-N(H)(CH_3)

- ↑ duratn of Actn as less susceptible for hydrolysis by MAO
- Lipid Soluble → BBB

* Methoxamine: H_3CO-[ring](OCH_3)-CH(OH)-CH(CH_3)-NH_2

* Amphetamine: [ring]-CH_2-CH(CH_3)-NH_2

دلوقتي احنا خلصنا حتة الـ Receptors دي صح وهنشتغل على الـ Neurotransmitt.

Adrinergic Neurotrans-mitters

OR

Adrinergic Agonists

ⓐ Catecholamines　　　　　ⓑ Noncatecholamines.

ⓐ Catecholamines

⊛ They are derivatives of β phenylethylamine　⌬ $-CH_2-CH_2-NH_2$

⊛ They are 3,4 dihydroxybenzene derivatives　HO ③ ② ① HO ④ ⌬ $-CH_2-CH_2-NH_2$ (catechol … amine.)

⊛ Catecholamines include : ① epinephrine
② norepinephrine
③ dopamine.　④ isoproterenol.

⊛ They are characterized by : ① high potency
② rapid inactivation by :

⊖ COMT postsynoptically , ⊖ MAO intraneuronally

⊖ COMT in gut wall , ⊖ MAO in Liver , gut wall

∴ has brief period of actn, when taken parentrally , ineffective orally.

* Catechol amines has poor penetratn,, in the CNS as they are polar, don't penetrate BBB.

ولوقتي نرسم الـ structures بتاعتهم هـ خليك ماشي معايا هتلاقيني كل خطوة بأزود 1group فبأعمل مركب جديد.

1. Dopamine — HO, HO-(ring)-$CH_2 - CH_2 - NH_2$
2. Norepinephrine — HO, HO-(ring)-$\underset{|}{\overset{OH}{CH}} - CH_2 - NH_2$ — زودت OH على الـ CH_2
3. epinephrine — HO, HO-(ring)-$\overset{OH}{CH} - CH_2 - N <^{H}_{CH_3}$ — زودت CH_3 على الـ (N)
4. isoproterenol — HO, HO-(ring)-$\overset{OH}{CH} - CH_2 - N <^{CH_3}_{CH_3}$ — زودت كمان CH_3 على الـ (N)

(1)–(3) → naturally occuring

* بص بقا هـ الـ (CH_3) اللي في الـ epinephrine والـ iso proterenol بتخليهم هـ more potent على الـ B هـ أكثر من الـ dopamine والـ Norepinephrine

(b) Non catecholamines

1. Phenylephrine — HO-(ring)-$\underset{OH}{CH} - CH_2 - N <^{H}_{CH_3}$
2. Ephedrine — (ring)-$\underset{OH}{CH} - \underset{CH_3}{CH} - N <^{H}_{CH_3}$
3. Methoxamine — H_3CO-(ring, OCH_3)-$\overset{OH}{CH} - \overset{CH_3}{CH} - NH_2$
4. Amphetamine — (ring)-$CH_2 - \underset{CH_3}{CH} - NH_2$

→ (Phenylephrine) شيك الـepinephrine بس عنده (OH) واحدة فقط على الـbenzene

→ less susceptible to hydrolysis by MAO ∴ longer actn, than catecholamines

, More Lipid sol. gives them access to CNS

Mechanism of Action

① Direct acting agonists:

حاجات بتدخل ← تمسك في الـ receptor وتعطي الـ effect ← directly.

- → Bind directly to adrenoceptors, produces effect.
- → they include all catechol amines, phenylephrine from non catecholamines.

② Indirect acting agonists:

بيدخل جوه الـ neuron ويعمل stimulate للـ release بتاع الـ NE اللي بيطلع ويمسك في الـ receptor ويعطي الـ effect.

- → those enter the presynaptic neuron, causes the release of norepinephrine in synaptic cleft → Binds to receptor → gives the effect
- → those include amphetamine, tyramine

③ Mixed acting agonists:

يعني ممكن يعمل كده وممكن يعمل كده.

- → Can bind directly to adrenoceptors → giving effect
- → Can cause the release of NE → binds → effect.
- → those include ephedrine, metaraminol.

ولو وقتي هنمسك الـ Direct acting ونتكلم عن خواص كل واحد فيهم شوية كده

Pray alot 4 US ...

(mechanism of Adrenergic Agonist)

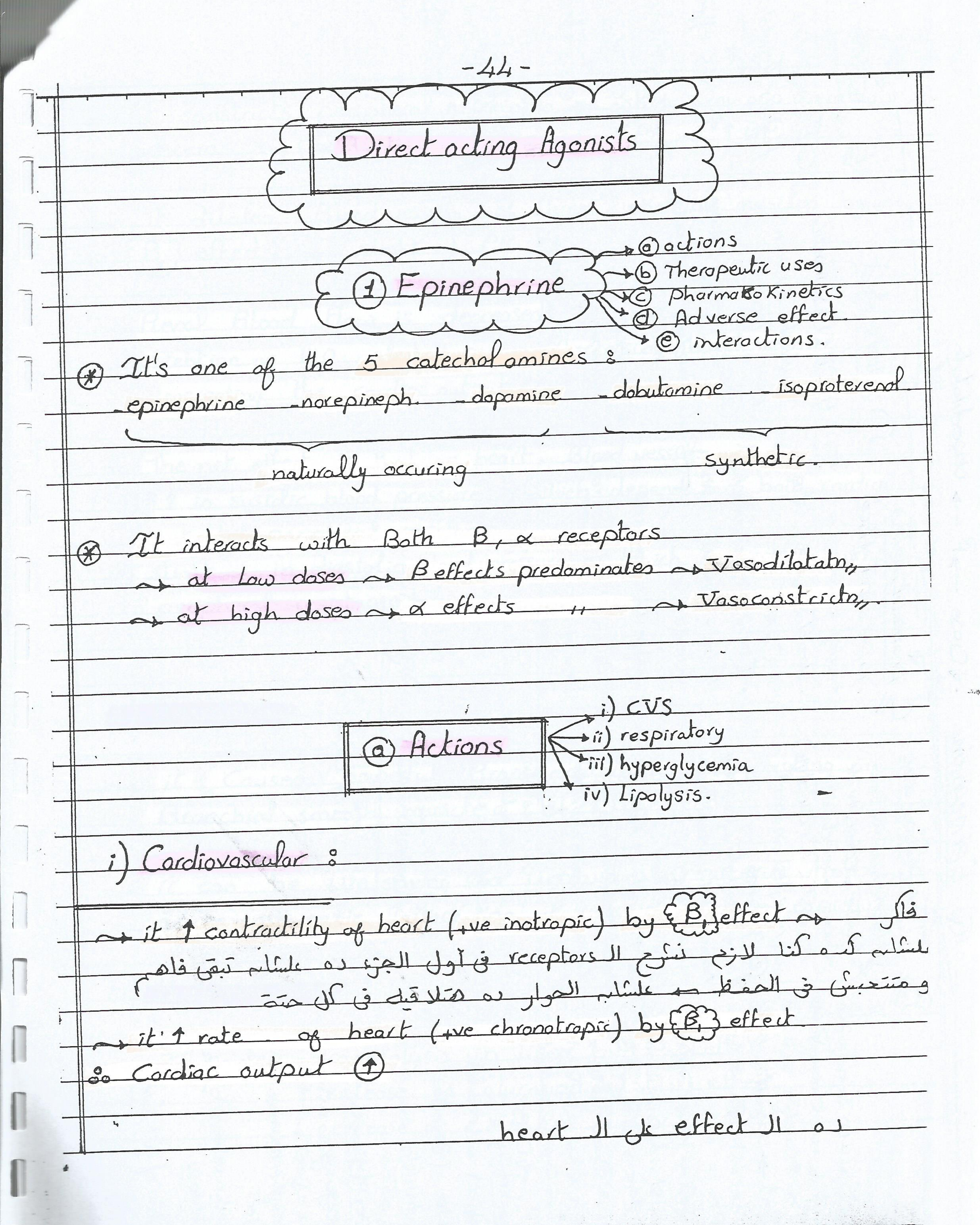
[A] Direct Acting Agonist

- Directly binds ē R → effect
- include Catechol amines - Phenyl Ephrin of non catecholamines

تعالوا نشوف اول → I * catecholamines.

① Epinephrine ② nor Ep. ③ Dopamine ④ Isoproterenol ⑤ dobutamine

- ①, ②, ③ → naturally occuring
- ④, ⑤ → synthetic



Direct acting Agonists

(1) Epinephrine

- (a) actions
- (b) Therapeutic uses
- (c) pharmacokinetics
- (d) Adverse effect
- (e) interactions.

(*) It's one of the 5 catecholamines :

- epinephrine - norepineph. - dopamine → naturally occuring
- dobutamine - isoproterenol → synthetic.

(*) It interacts with Both β, α receptors

→ at low doses → β effects predominates → vasodilatation
→ at high doses → α effects " → vasoconstriction.

(a) Actions

- i) CVS
- ii) respiratory
- iii) hyperglycemia
- iv) Lipolysis.

i) Cardiovascular :

→ it ↑ contractility of heart (+ve inotropic) by β_1 effect → فاكر علشان كده كنا لازم نشرح الـ receptors في أول الجزء ده علشان تبقى فاهم ومتتحبسش في الحفظ — علشان الحوار ده هتلاقيه في كل حتة

→ it ↑ rate of heart (+ve chronotropic) by β_1 effect

∴ Cardiac output ↑

ده الـ effect على الـ heart

① Epinephrine

- ↓ Dose → β → Vasodilatation
- ↑ → α → Constriction

A. Action

① CVS
- β_1 effect → +ve Ionotropic (contractility) → +ve Chronotropic (Rate) → ↑ Cardiac output
- β_2 effect → Vasodilatation of BVs → liver & skeletal muscles → ↓ PR
- α_1 effect → vasoconstriction of BVs → skin & viscera & mucous membrane → ↑ PR → ↑ BP
- ↓ Renal Blood flow → ↑ Retention of H_2O - electrolytes → BV↑ → cardiac output ↑
- ↑ SBP • ↓ D.BP

② Respiratory s
- β_2 effect → smooth muscles of Bronchai Vasodilatation so TTT of asthma.

③ Hyperglycemia
- ↑ glycogenolysis in liver by β_2 effect
- ↑ glucagon release by β_2 effect
- ↓ insulin release by α_2

④ Lipolysis
- lipolysis of adipose Tissue by β_1 effect

B. Therapeutical uses

① Bronchial asthma
- acute → Epinephrine
- chronic → Selective β_2 Agonist (Terbutaline) as no effect on Heart

② glucoma
- as ↓ production of aqueous humour by vasoconstriction of cilary body BVs by α_1

③ ē anesthestics
- To ↑ duration of Action of Local anesthestics as it makes vasoconstriction at The site of injection So allow local anesthetics To persist at ḍ site before absorption in systemic ci.

C. pharmacokinetics

- rapid onset of Action
- brief duration
- deactivated by MAO & COMT
- I.V & S.C . endotracheal Tube - Inhalation - Topically in eye
- ineffective orally as deActivated by intestinal enzymes.

D. Adverse effect

① CNS Disturbance
Headach. Tension fear - Tremors

② pulmonary edema

③ Cardiac errythema (digitalis)

④ Cerebral Hemorrage
↑ BP → ↑ PR α_1

E. interAction

① Epinephrine + Hyper Thyroidism drugs
→ ↑ CVS effect

② Epinephrine + Cocaine
→ ↑ CVS effect
as Cocaine prevent ↓ upTake of neuron for E. So it bind ē R for long Time

* Selective β_2 Agonist *

Terbutaline

→ it constricts peripheral arterioles of skin, mucous membrane, viscera by α_1 effect → causes ↑ PR → ↑ BP

→ it dilates Blood vessels of Liver, skeletal muscles by β_2 effect → slight ↓ PR

→ Renal Blood flow is decreased
∴ retention of H_2O, electrolytes → increasing blood volume → increasing the cardiac output.

∴ The net effect of that on heart, Blood vessels is:
1. ↑ in systolic blood pressure → which depends on both cardiac output, peripheral resistance.
2. slight ↓ in diastolic blood pressure → which depends only on peripheral resistance.

ii) Respiratory :

→ it Causes powerful Bronchodilatation by acting on Bronchial smooth muscle by β_2 effect

→ it can be Life saving in individuals suffering from acute asthmatic attack as it releives dyspnea rapidly

iii) Hyperglycemia :

→ it causes glucogenolysis in Liver by β_2 effect (→ Breaking ↓ glucogen → glucose)
→ " " ↑ release of glucagon by β_2 effect.
→ " " ↓ release of insulin by α_2 effect.

iv) Lipalysis :

→ it causes Lipolysis from adipose tissue by {β_1}, {β_3} effects

لو مناكر الحتة بتاعت الـ receptors فى page (39) كويس مش هتتعب خالص فى حفظهم هنا ← هتلاقيهم سهلين جداً.

(b) Therapeutic uses
- i) Bronchospasm
- ii) Glucoma.
- iii) Local anaesthetics.

i) Bronchospasm :

→ epinephrine is the primary drug in emergency treatment of acute asthma. , anaphylactic shock.

→ {however} → Selective β_2 agonist as terbutaline are favoured (prefered) in treatment of chronic asthma as it has no effect on heart, has longer duratn of actn.

↓ علشان الـ heart عليه (β_1) فقط

أنا عايز أعالج العيان ← أديله حاجة selective علشان متعبش الـ heart معايا ← هو مالوش ذنب
← الـ epinephrine مش selective ← مقدرش أستخدمه فى العيان الـ chronic
لكن ممكن أستخدمه فى العيان الـ acute لأن حالته صعبة ومحتاج دواء قوى
وهو الـ epinephrine

ii) Glucoma :

→ epinephrine is used to reduce intraocular pressure (IOP) in open angle glucoma as it reduces production of aqueous humour by vasoconstrictn of ciliary body blood vessels by α_1 effect

يعني مش الـ ciliary body نفسه هو اللي بيحصله constrictn
لكن الـ bloodvessels هي اللي بيحصلها vasoconstrictn

← لذلك الـ blood flow بيقل ← لذلك الـ ciliary body يقل تصنيعها للـ aqueous humour

iii) Anaesthetics :

→ anaesthetics soln contain 1 : 100,000 parts of epinephrine

طيب ليه بنحط الـ epinephrine مع الـ anaesthetics
← علشان أعمل vasoconstrictn في المنطقة اللي أنا هطبق فيها الـ anaesthetics فالـ blood flow للمنطقة دي بيقل ← لذلك الـ anaesthetics تفضل في مكانها ← فتفضل مخدرة المكان ده.

تعالوا نقول الكلمتين دول بقى باللغة ← 1o1ooo

→ The effect of epinephrine is to ↑ the duratn of local anaesthetics
→ this is done by vasoconstrictn at site of injection so allowing the local anaesthetics to persist at the site befor being absorbed into circulation & metabolized.

→ also used to vasoconstrict mucous membranes to control oozing of capillary blood

الناس اللي بتنزف من أنفها ← نحط epinephrine يعمل vasoconst. ← يوقف النزيف.

(c) PharmacoKinetics

→ epinephrine has rapid onset of actn,
{But} Brief duratn, of actn.

→ it's given intravenously For most rapid actn,.
→ also can be given → Subcutaneously or, endotracheal tube or, by inhalatn, or topically in eye.
→ oral administratn, is ineffective since all catecholamines are inactivated by intestinal enzymes.

(d) Adverse effects

→ i) CNS
→ ii) haemorrhage
→ iii) cardiac arrhythmias
→ iv) Pulmonary oedema.

i) CNS disturbances :

* anxiety * fear * tension * headache * tremors.

ii) Haemorrhage :

→ it may induce cerebral haemorrhage as ① their vessels are very thin, ② due to ↑ BP

iii) Cardiac arrhythmiasis : → especially if patient is receiving digitalis

iv) Pulmonary edema

© Interactions

→ i) hyperthyroidism
→ ii) Cocaine

i) Hyperthyroidism :

→ epinephrine → may have enhanced CVS actn. in patients with hyperthyroidism.
∴ if it's required in such patient → the dose must be reduced.

ii) Cocaine :

→ epinephrine → may produce ↑ CVS actn. in presence of Cocaine
because Cocaine prevent the uptake of catecholamine into the neuron
So, it remains at the receptor site for longer period.

كده إحنا خلصنا الـ epinephrine خالص
← اتفقنا إن الكلام كله سهل ومش معقد.

Levorterenol (2) Norepinephrine

→ actions
→ Therapeutic uses.

→ it affects α receptors more than β receptors
علشان مفيهاش (CH_3)

→ Norepinephrine is called also {levorterenol}

② nor Epinephrine [levorterenol]

- more potent for α Recepter as it not contain CH_3 gp

A Actn

- α_1 effect → vasoconstrictn ↑PR → ↑BP
- ↓B flow to kidney
- ↑SBP • ↑DBP

N.B Baroceptors found in aortic arch and carotid artery. These Recepter feel B-P if ↑BP so send impulses to CNS → impulses by vagal nerve to Heart to ↓Rate (chronotropic)
not Affect contractility (inotropic)
But if muscarinic R of Heart Blocked (Atropine) so vagal impulses not reach to Heart
→ Tachy cardia
This called
Effect of Atropine pre III

B Therapeutical uses

III of shock as ↑BP and ↑vascular R
But Dopamine more preferred why ??
as it doesn't ↓ kidney Blood flow -

(a) actions → i) CVS

→ Vasoconstrictn : it causes rise in peripheral resistance due to vasoconstrictn of most vascular beds including the Kidney by α_1 effect

∴ → Both systolic, diastolic blood pressure increase.

→ Baroceptor reflex :

* we have baroceptor which are present in aortic arche, carotid artery
* those receptors feel the blood pressure
* if it ↑ → those receptors send impulses to CNS which send impulses to the heart through vagal nerve to ↓ its rate.
* this action counteracts the Local actions of norepinephrine on heart although it doesn't affect the positive inotropic effects on heart.

→ if we block the M receptors of heart → the vagal impulse won't reach the heart → then the effect of norepinephrine will appear as tachycardia, this is Known as effect of atropine pretreatment

(b) Therapeutic effects

→ it's used to treat shock as it ↑ BP by ↑ vascular resistance.

But → dopamine is better as it doesn't reduce the blood flow to the Kidneys as norepinephrine does.

③ Isoproterenol (Isoprenaline)

Epinephrine ⟶ ...

- synthetic Catecholamines
- more potent for **B** R as contain CH_3 gp. less selective for B_1, B_2 R

A Actn

① CVS

- +ve Ionotropic B_1
- +ve Chronotropic
- +↑ Cardiac output
- ↑SBP - ↓DBP
- ↓ mean arterial BP

② Respiratory S.

Broncho Dilatn B_2 by inhalatn

③ hyperglycemia

④ lipolysis

B Therapeutic use

① Acute Pulmonary asthma

② Heart stimulant in emergency situatn

C Pharmacokinetics

- Parentarlly
- inhallatn
- Sublingual
- deActivated by COMT

resistant to MAO

D Adverse effect

① CNS disturbance

② Pulmonary edema

③ Cerebral Hemorrage

④ Cardiac erythema -

③ Isoproterenol

→ ⓐ actions
→ ⓑ Theropeutic uses.
→ ⓒ PharmacoKinetics
→ ⓓ adverse effects.

* it's direct, synthetic catecholamines.
* it stimulates β_1, β_2 with low selectivity. (disadvantage)
* its action on α receptors is insignificant.

ⓐ Actions

→ i) Cardiovascular
→ ii) respiratory.
→ iii) others.

i) Cardiovascular :

→ it ↑ rate, Force of contractility
∴ ↑ Cardiac output. (β_1)

→ it dilates the arterioles of skeletal muscles (β_2)
∴ it ↓ peripheral resistance.

→ ∴ it ↑ systolic BP, ↓ diastolic BP, ↓ the mean arterial BP.

ii) Pulmonary :

→ Bronchodilatn (β_2) effect → used in asthma (acute)
→ it's taken by inhalatn

iii) other effects :

→ other actions on β receptors as :
↑ Blood sugar, ↑ Lipolysis.
But they aren't significant clinically.

(b) Therapeutic uses

* (*) it's now rarely used as bronchodilator in asthma.
* (*) it can be used as heart stimulant in emergency situations

(c) PharmacoKinetics

absorptn :

- it's absorbed systemically by sublingual mucosa
- it's more " " " parentral route, inhalatn,

Metabolism :

- it's a Marginal Substrate for COMT
- it's stable to MAO

(d) Adverse effects

- Similar to that of epinephrine.
  1. CNS disturbances
  2. haemorrhage.
  3. Cardiac arrhythmiasis
  4. Pulmonary edema.

④ Dopamine

- it is immediate precursor of N-E (HO, HO–[ring]–CH_2-CH_2NH_2 —DA hydroxylase→ HO, HO–[ring]–CH-CH_2NH_2, OH NE)
- naturally occured in basal ganglia and DA adrenal medulla secretn
- ↓ Dose → β Recepter → Vaso dilatatn (cardiac)
- ↑ Dose → α " → " constrictn
- not only α, β Recepter But also D_1 - D_2 R < in mesentry, renal vascular beds - why??
  - ↳ presynaptic

A Actn

+ve Ionotropic
+ve Chronotropic } β_1
↑ C. output

- α_1 → Vaso constrictn
- D_1, D_2 → Dilatatn ↑ renal B flow

N.B D_1, D_2 not affected ē α, β Blocker

B Therapeutical use

① Tt of shock where required ↑ Heart Activity ē out stop Renal functn

N.B Dopamine more preferred Than epinephrine

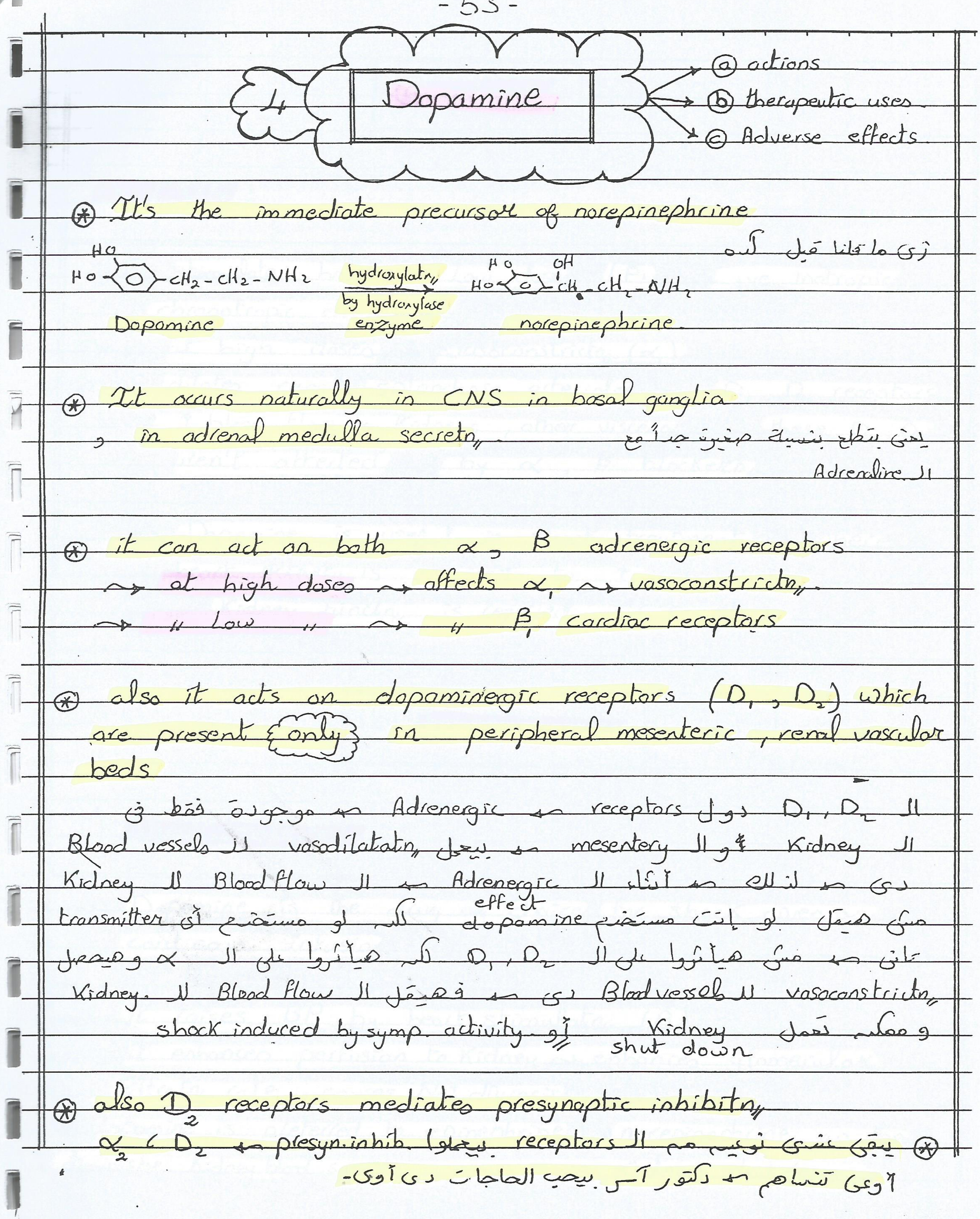
C Adverse effect

D Pharmacokinetics → Short half life

- rapidly metabolized into Homovanillic a.

↓

Nausea
Vomiting
Arrythema -



4 Dopamine

→ ⓐ actions
→ ⓑ therapeutic uses.
→ ⓒ Adverse effects.

⊛ It's the immediate precursor of norepinephrine

دي ما قلنا قبل كده

HO(HO)-C₆H₃-$CH_2-CH_2-NH_2$ (Dopamine) —hydroxylation by hydroxylase enzyme→ HO(HO)-C₆H₃-CH(OH)-$CH_2-CH_2-NH_2$ (norepinephrine).

⊛ It occurs naturally in CNS in basal ganglia, in adrenal medulla secretion.

يعني بتطلع بنسبة صغيرة جداً مع ال Adrenaline.

⊛ it can act on both α, β adrenergic receptors
→ at high doses → affects α_1 → vasoconstriction.
→ " low " → " β_1 cardiac receptors

⊛ also it acts on dopaminergic receptors (D_1, D_2) which are present {only} in peripheral mesenteric, renal vascular beds

ال D_1, D_2 دول receptors ← Adrenergic ← موجودة فقط في
ال Kidney & وال mesentery ← بيعمل vasodilatation لل Blood vessels
دي ← لذلك ← أثناء ال Adrenergic ← ال Blood flow لل Kidney
مش هيقل لو إنت مستخدم dopamine effect لكن لو مستخدم أي transmitter
تاني ← مش هيأثروا على ال D_1, D_2 لكن هيأثروا على ال α وهيعمل
vasoconstriction لل Blood vessels دي ← فهيقل ال Blood flow لل Kidney.
وممكن تعمل Kidney shut down أو shock induced by symp. activity

⊛ also D_2 receptors mediates presynaptic inhibition.

⊛ يبقى عشان نوضح ← ال receptors بيعملوا presyn. inhib. ← α_2, D_2
أوعى تتساهم ← دكتور آس بيحب الحاجات دي أوي.

ⓐ actions → i) CVS

i) CVS :

* → stimulate heart in low doses (β_1) → +ve inotropic, chronotropic effect.
* → at high doses → vasoconstrictn (α_1)
* → dilates renal, splanchnic arterioles → D_1, D_2 receptors
∴ ↑ blood flow to kidneys, other viscera. → these D_1, D_2 aren't affected by α, β blockers.

∴ Dopamine is useful in shock treatment → where → heart activity is required to ↑
, → Kidney functn is required not to stop.

ⓑ Therapeutic uses → i) shock treatment.

i) Shock treatment :

→ Dopamine is the drug of choice for shock given as continous infusion

→ it raises BP by heart stimulatn (β_1)
, it enhances perfusion to kidney → enhances glomerular filtratn rate, causes Na^+ diuresis
∴ dopamine is preferred to epinephrine, norepinephrine as they diminishe kidney blood supply, may cause kidney shutdown.

(c) Adverse effects

(*) → Dopamine overdose produces sympathetic then it's rapidly metabolized to homovanillic acid whose adverse effects are :

1. Nausea
2. hypertension.
3. Arrythmiasis

↓ ∴ short - Lived action.

احنا عارفين إن كده استهبال و المحاضرة كده ملهاش حل
كلكم — السنة اللى فاتت أخدتوا المنهج فى ١٣ محاضرة واحنا
هناخد ١١ محاضرة فقط

— لذلك المحاضرة دى تقدر تعتبرها محاضرتين — محاضرة ٣٦ صفحة
والأخرى ٢٠ صفحة — علشان تهون على نفسك — لكن لو اعتبرتها
محاضرة واحدة ٥٥ صفحة هتتعقد ومش هتقدر تذاكرها.

— وبتقسيم الجزء الأول بيتكلم عن موضوع الـ Anti-cholinergic agents
والجزء الثانى بيتكلم عن الـ adrenergic agonists , Adrenergic receptors

— يعنى مش هتخسر حاجة لو قسمت المحاضرة إلى جزئين — ده علشان نفسك
نصيحة أخوية يعنى.

— وأخيراً — أرجوكم أرجوكم — طلبنا المختار : ادعوا لنا — بتفوق
معانا جداً جداً جداً

Dr. / K. A. Dr. / P. S.

⑤ Dobutamine

- Synthetic Catecholamines
- Selective β_1 Receptor

A. Actn

- β_1 effect →
  ↑ Cardiac out put ē little ↑ in Heart rate
  ∴ CoP = Strock Volum × HR
  (CoP ↑, HR ↑)
  ↓
  ∴ ↑ Strock Volum

This is imp. in Coronary artery problems

So it Doesn't ↑ O_2 demands of myocardium

Adv over all sympathomimetics

B. Therapeutical use

↑ C.O.P - ↑HR → in Congestive Heart failure

C. adverse effect

- Epinephrin Ad.
  - CNS disterbance
  - Pulmery edema
  - arryThema
  - cerebral Hemorrage

Used ē Caution ē Case (arterial fibrillatn) due To ↑ A-V conductn

Selective

- β_1 → dobutamine
- β_2 → Terbutaline

↓↓ C-HF